



Implicazioni riproduttive dei trattamenti per CIN

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A.G.E.O. - 3° corso di aggiornamento in Ginecologia e Ostetricia
22-23 novembre 2019 - Bologna

Introduzione 2.

The average age of a **woman diagnosed and treated for CIN** is between **25 and 30 years** of age

LEEP (loop electrosurgical excision procedure)/**LLETZ** (large loop excision of the transformation zone) is the **most widely cervical excision procedure** currently used

Possible adverse effects on future fertility and pregnancy outcomes is an active research area

Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PP, Arbyn M, Bennett P, Paraskevaidis E. *Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease*. Cochrane Database Syst Rev. 2017 Nov 2;11.

Zhuang, H., Hong, S., Zheng, L., Zhang, L., Zhuang, X., Wei, H., & Yang, Y. *Effects of cervical conisation on pregnancy outcome: a meta-analysis*. Journal of Obstetrics and Gynaecology, 2019 Jan;39(1):74-81

Outcomes ostetrici

Outcomes materni

- Aborto
- Parto Pretermine
- Rottura Prematura Pretermine delle Membrane

Outcomes fetali

- Basso peso alla nascita
- Ricovero in TIN
- Mortalità Perinatale

Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PP, Arbyn M, Bennett P, Paraskevaidis E. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. Cochrane Database Syst Rev. 2017 Nov 2;11:CD012847. doi: 10.1002/14651858.CD012847.

Ciavattini A, Clemente N, Delli Carpini G, Gentili C, Di Giuseppe J, Barbadoro P, Prospero E, Liverani CA. Loop electrosurgical excision procedure and risk of miscarriage. Fertil Steril. 2015 Apr;103(4):1043-8.

Outcomes ostetrici

Outcomes materni

➤ Parto Pretermine

Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PP, Arbyn M, Bennett P, Paraskevaidis E. *Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease*. Cochrane Database Syst Rev. 2017 Nov 2;11:CD012847. doi: 10.1002/14651858.CD012847.

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Parto pretermine 1.

.....Il rischio è significativamente aumentato dopo trattamento per CIN

- | | |
|--------------------------|-------------------------------------|
| • Prematurity < 37 w: | RR 1.75 (95% CI 1.57 – 1.96) |
| • Prematurity < 32-34 w: | RR 2.25 (95% CI 1.79 – 2.82) |
| • Prematurity < 28-30 w: | RR 2.23 (95% CI 1.55 – 3.22) |

Parto pretermine 2.

...il rischio è maggiore per i trattamenti **escisionali** rispetto a quelli ablativi...

- **Excision versus no treatment:** RR 1.87 (95% CI 1.64 – 2.12)
- **Ablation versus no treatment:** RR 1.35 (95% CI 1.20 – 1.52)

Parto pretermine 3.

Patient or population: women with known obstetric outcomes

Setting: hospitals/ clinics

Intervention: treatment for CIN before pregnancy

Comparison: women with no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N of participants (studies)	Quality of the evidence (GRADE)
	Risk with [comparison]	Risk with [Intervention]			
PTB (< 37 w)	Study population		RR 1.75 (1.57 to 1.96)	5,242,917 (59 observational studies)	⊕○○○ VERY LOW ¹
	54 per 1000	95 per 1000 (85 to 106)			
PTB (< 32 to 34 w)	Study population		RR 2.25 (1.79 to 2.82)	3,793,874 (24 observational studies)	⊕○○○ VERY LOW ²
	14 per 1000	32 per 1000 (26 to 40)			
PTB (< 28 to 30 w)	Study population		RR 2.23 (1.55 to 3.22)	3,910,629 (8 observational studies)	⊕○○○ VERY LOW ³
	3 per 1000	7 per 1000 (5 to 11)			
PTB (< 37 w) - Repeat cones versus No Treatment	Study population		RR 3.78 (2.65 to 5.39)	1,317,284 (11 observational studies)	⊕○○○ VERY LOW ⁴
	41 per 1000	156 per 1000 (109 to 222)			
pPROM (< 37 w)	Study population		RR 2.36 (1.76 to 3.17)	477,011 (21 observational studies)	⊕○○○ VERY LOW ⁵

Parto pretermine 4.

Il rischio è legato alla **modalità di escissione**

- **CKC versus no treatment:** RR **2.70** (95% CI 2.14 – 3.40)
 - **LC versus no treatment:** RR **2.11** (95% CI 1.26 – 3.54)
 - **LEETZ versus no treatment:** RR **1.58** (95% CI 1.37 – 1.31)
-
- **Excision versus no treatment:** RR **1.87** (95% CI 1.64 – 2.12)

Parto pretermine 5.

Il rischio è legato alla profondità del cono

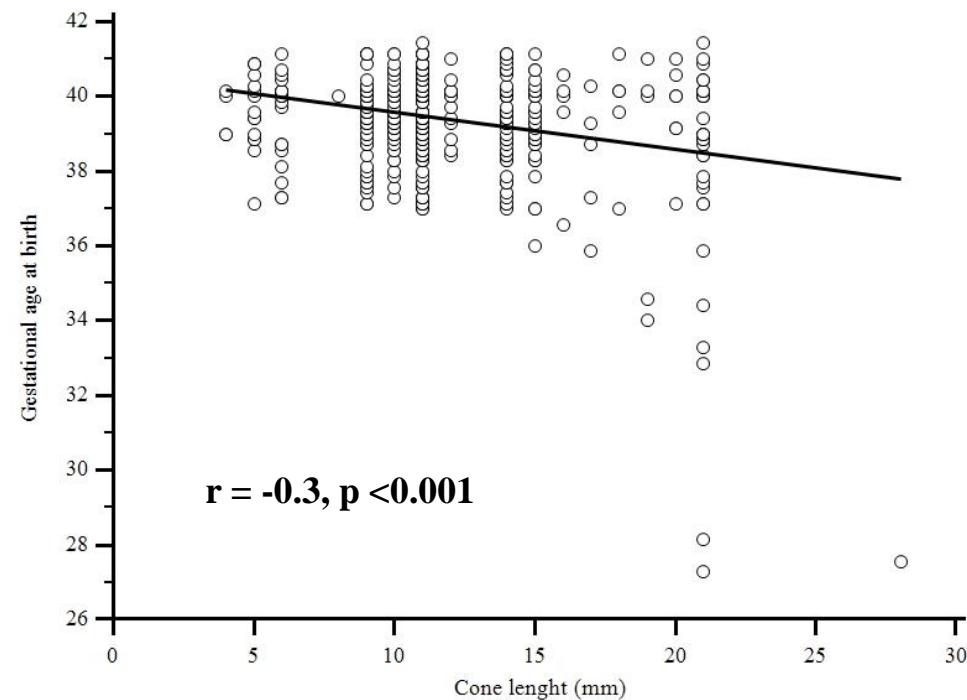
- Cone depth \leq 10-12 mm: RR 1.54 (95% CI 1.09 – 2.18)
- Cone depth \geq 10-12 mm: RR 1.93 (95% CI 1.62 – 2.31)
- Cone depth \geq 15-17 mm: RR 2.77 (95% CI 1.95 – 3.93)
- Cone depth \geq 20 mm: RR 4.91 (95% CI 2.06 – 11.68)

Parto pretermine 6.

Length but not transverse diameter of the excision specimen for high-grade cervical intraepithelial neoplasia (CIN 2-3) is a predictor of pregnancy outcome

Carlo A. Liverani^a, Jacopo Di Giuseppe^b, Nicolò Clemente^b,
Giovanni Delli Carpini^b, Ermelinda Monti^a, Fabiana Fanetti^a, Giorgio Bolis^a
and Andrea Ciavattini^b

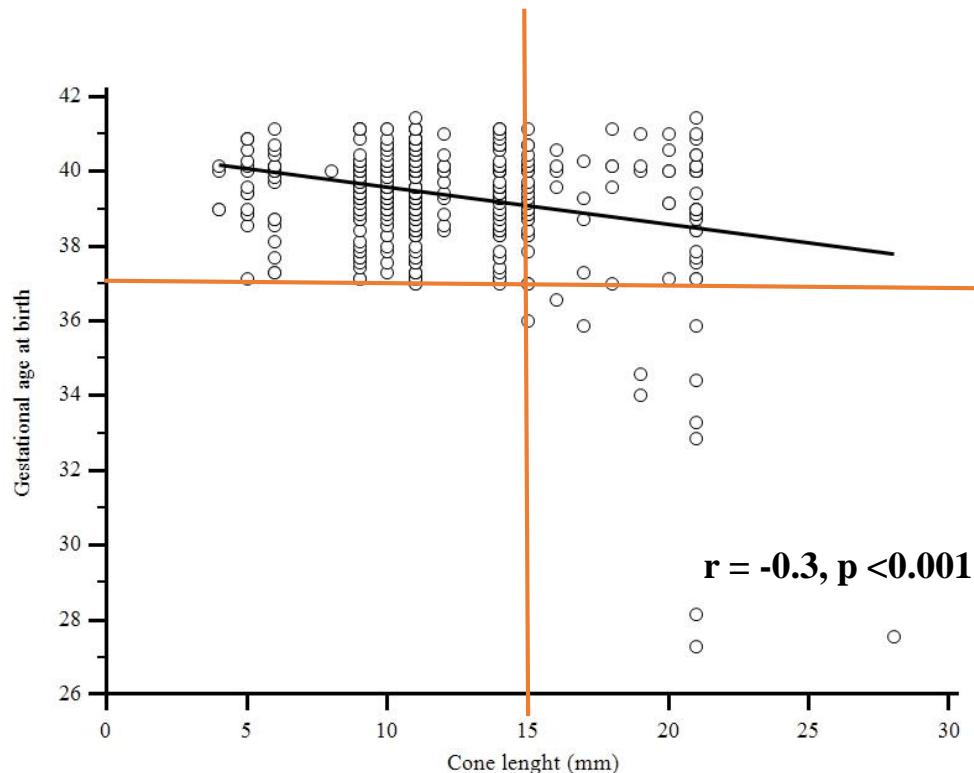
A linear inverse correlation ($r = -0.3$, $p <0.001$) between gestational age at birth and lenght, but not volume ($r=0.0$, $p =0.9$) or transverse diameter, emerged



Parto pretermine 6.

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Liverani CA, Di Giuseppe J, Clemente N, Delli Carpini G, Monti E, Fanetti F, Bolis G, Ciavattini A. Length but not transverse diameter of the excision specimen for high-grade cervical intraepithelial neoplasia (CIN 2-3) is a predictor of pregnancy outcome. Eur J Cancer Prev. 2015 Aug 27.

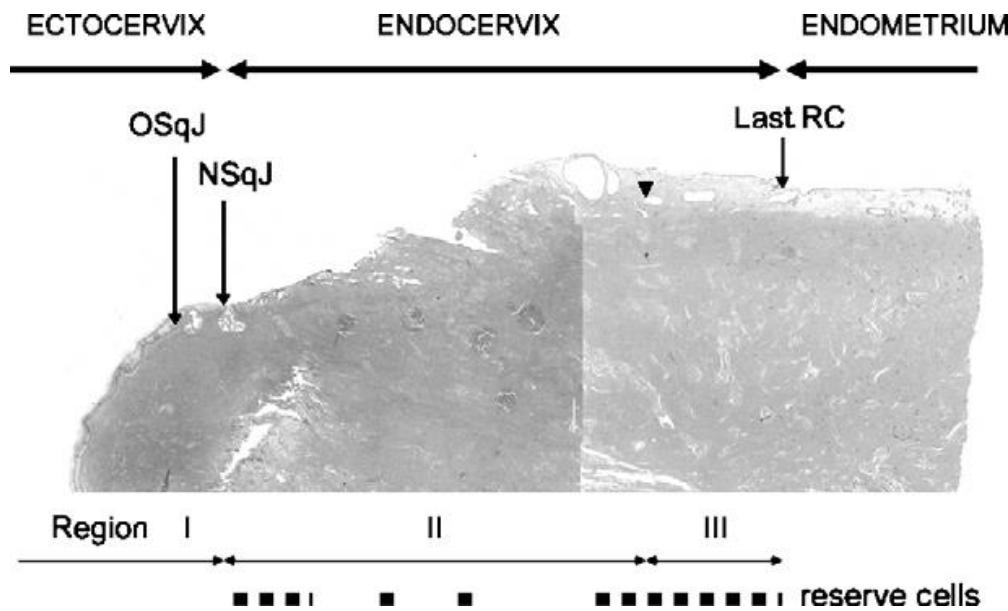
Parto pretermine 7.

..... con l'escissione si realizza un **danno cervicale anatomico-funzionale e strutturale**:

- **Riduzione della lunghezza cervicale con compromissione dell'integrità**
- **Modificazioni strutturali nella distribuzione del collagene nella porzione sana e riduzione dei meccanismi di supporto meccanico**

Parto pretermine 8.

I processi di rigenerazione post trattamento escisionale sono mediati dalle **cellule epiteliali** – cellule di riserva del canale cervicale - che interagiscono in un network con le **cellule stromali/mesenchimali** (miofibroblasti)



..... an **increasing cone length** might imply a greater involvement of the cervical canal, with **greater destruction of cervical reserve cells** and consequent inability to regenerate and repair properly...

Parto pretermine 9.

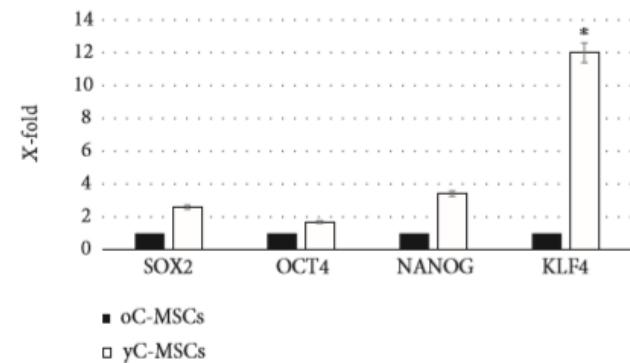
Research Article

Mesenchymal Stem Cells from Cervix and Age: New Insights into CIN Regression Rate

Monia Orciani ,¹ Miriam Caffarini ,¹ Raffaella Lazzarini ,¹ Giovanni Delli Carpini ,² Dimitrios Tsiroglou ,² Roberto Di Primio ,¹ and Andrea Ciavattini ,²

A mesenchymal stem cell (MSC) population persists inside the cervix and this cell population displays age-related properties.

Considering as 1 the expression detected in MSCs from old cervixes, the same genes are from 1.74 ± 0.21 (OCT4) up to 12.05 ± 0.53 (KLF4) fold higher in MSCs from young patients

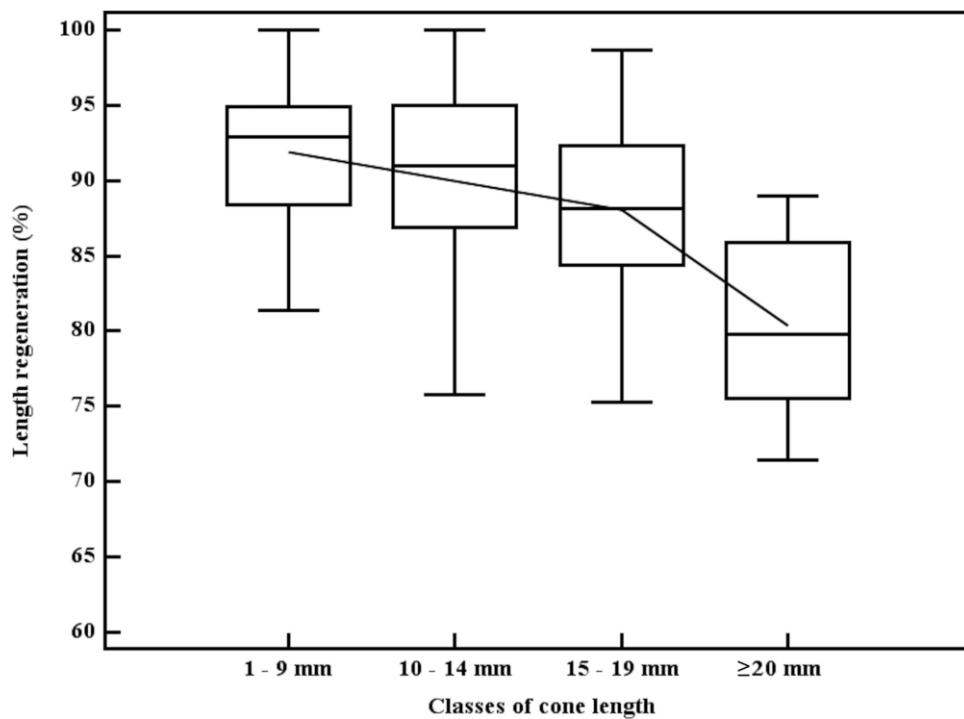


Parto pretermine 10.

BMJ Open Effect of age and cone dimensions on cervical regeneration: an Italian multicentric prospective observational study

Andrea Ciavattini,¹ Giovanni Delli Carpini,¹ Lorenzo Moriconi,¹ Nicolò Clemente,¹ Nina Montik,¹ Rosa De Vincenzo,² Anna Del Fabro,³ Monica Buttignol,³ Caterina Ricci,² Francesca Moro,² Francesco Sopracordevole³

..... women with a **cone length < 15 mm** presented a **significant higher length regeneration**, after six months, than women with a cone length ≥ 15 mm (**90.7% \pm 5.9%** vs **86.9% \pm 6.5%**, P<0.001)



Outcomes ostetrici

Outcomes materni

➤ pPROM

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pPROM 1.

Patient or population: women with known obstetric outcomes

Setting: hospitals/ clinics

Intervention: treatment for CIN before pregnancy

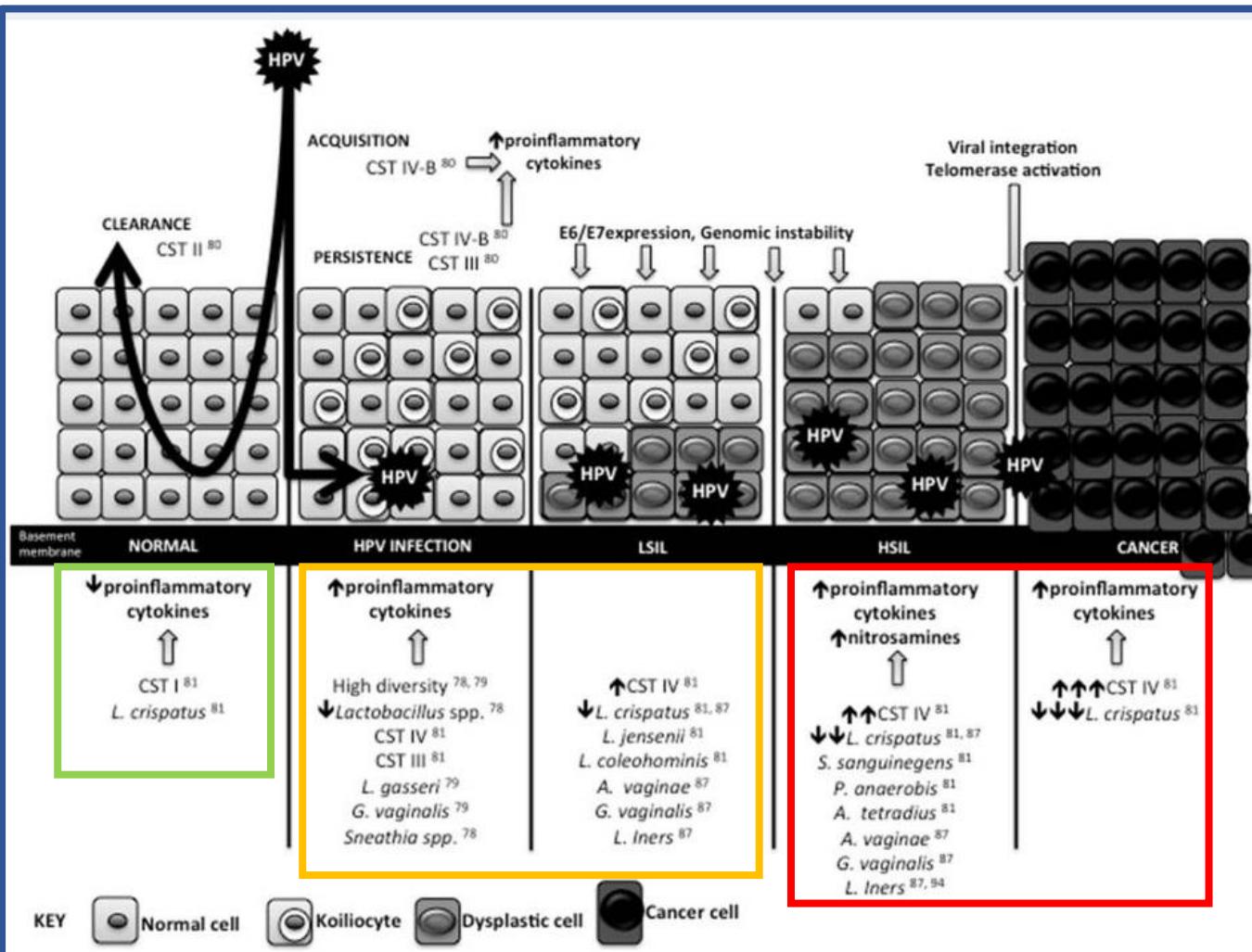
Comparison: women with no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N of participants (studies)	Quality of the evidence (GRADE)
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pPROM e Corionamniotite 2.

Il rischio di rottura prematura pretermine delle membrane (<37 w: 21 studi, 477011 donne) 6.1% vs 3.4%, RR 2.36, IC 95% 1.76-3.17) e corionamniotite (4 studi, 29198 donne; 3.5 vs 1.5%; RR 3.43, IC 95% 1.36-8.74) risulta essere aumentato dopo trattamento escisionale.

Microbiota vaginale



There is a wealth of emerging evidence to suggest that the cervico-vaginal bacterial population plays a substantial role in the persistence of the virus and the presence of subsequent cervical pre-invasive disease.

Outcomes ostetrici

Outcomes materni

➤ Aborto

Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PP, Arbyn M, Bennett P, Paraskevaidis E. *Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease*. Cochrane Database Syst Rev. 2017 Nov 2;11:CD012847. doi: 10.1002/14651858.CD012847.

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Loop electrosurgical excision procedure and risk of miscarriage

Andrea Ciavattini, M.D.,^a Nicolò Clemente, M.D.,^a Giovanni Delli Carpini, M.D.,^a Chiara Gentili, M.D.,^a Jacopo Di Giuseppe, M.D.,^a Pamela Barbadoro, M.D.,^b Emilia Prospero, M.D.,^b and Carlo Antonio Liverani, M.D.^c

La LEEP sembra essere associata ad un sensibile aumento del rischio di aborto spontaneo

18.1% vs 12.8% (trattate vs non trattate)

OR 1.78, 95% IC 1.24-2.95, p = 0.003

Aborto spontaneo

.....Women with a time interval from LEEP to pregnancy of **<12 months** are at increased risk for miscarriage.....

Risk of spontaneous miscarriage for women with time interval of <12 months compared with ≥12 months from LEEP to pregnancy.

Outcome	LEEP-to-pregnancy interval		OR (95% CI)	Adjusted OR (95% CI) ^a	P value
	<12 mo (n = 142)	≥12 mo (n = 498)			
Miscarriage (<24 wk of gestation)	40 (28.2)	76 (15.3)	2.18 (1.40–3.38)	2.28 (1.36–3.56)	<.001
Early miscarriage (<12 wk of gestation)	34 (23.9)	61 (12.2)	2.26 (1.41–3.61)	2.43 (1.50–3.93)	<.001
Late miscarriage (12–24 wk of gestation)	6 (4.2)	15 (3.0)	1.42 (0.54–3.73)	1.36 (0.51–3.60)	.54

* Adjusted for age, nulliparity, previous spontaneous abortion, smoking, and BMI.

Clavattini. Risk of miscarriage after LEEP. Fertil Steril 2015.

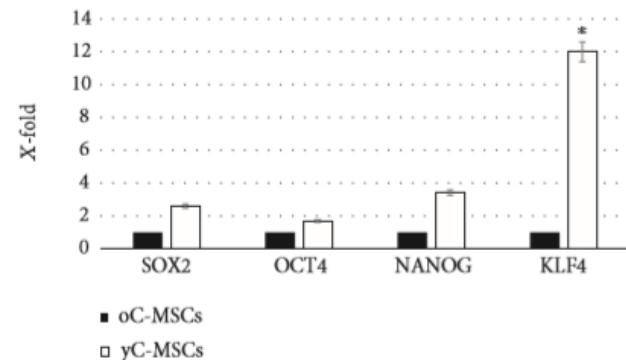
I processi di **rimodellamento cervicale** dopo terapia escisionale potrebbero essere associati al rischio aumentato di **aborto**

Research Article

Mesenchymal Stem Cells from Cervix and Age: New Insights into CIN Regression Rate

Monia Orciani ,¹ Miriam Caffarini ,¹ Raffaella Lazzarini ,¹ Giovanni Delli Carpini ,² Dimitrios Tsiroglou ,² Roberto Di Primio ,¹ and Andrea Ciavattini ,²

..... compared to oC-MSCs, MSCs from cervixes of young patients exhibited significantly ($p < 0.05$) higher levels of IL2, IL6, IL10, IL12, IFN- γ , and TGF- β .



Modalità del parto

Mode of delivery

Length of labour

Use of analgesia

Rate of induction of labour

Cervical stenosis

Haemorrhage

were not affected
by treatment

The rate of **cervical cerclage insertion** was **higher for treated** than non-treated women (eight studies, 141 300 women, 4.0% vs 0.7%, relative risk 14.29, 95% confidence interval 2.85 to 71.65)

Outcomes ostetrici

Outcomes fetalì

- Basso peso alla nascita
- Ricovero in TIN
- Mortalità Perinatale

Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PP, Arbyn M, Bennett P, Paraskevaidis E. *Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease*. Cochrane Database Syst Rev. 2017 Nov 2;11:CD012847. doi: 10.1002/14651858.CD012847.

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Outcomes feto/neonatali

Outcomes	Anticipated absolute effects ⁺ (95% CI)		Relative effect (95% CI)	% of participants (studies)
	Risk with No Treatment	Risk with Treatment		
LBW (< 2500 g) - Treatment versus No Treatment	Study population		RR 1.81 (1.58 to 2.07)	1,348,206 (30 observational studies)
	37 per 1000	66 per 1000 (58 to 76)		
NICU Admission - Treatment versus No Treatment	Study population		RR 1.45 (1.16 to 1.81)	2557 (8 observational studies)
	89 per 1000	130 per 1000 (104 to 162)		
Perinatal Mortality - Treatment versus No Treatment	Study population		RR 1.51 (1.13 to 2.03)	1,659,433 (23 observational studies)
	7 per 1000	11 per 1000 (8 to 14)		

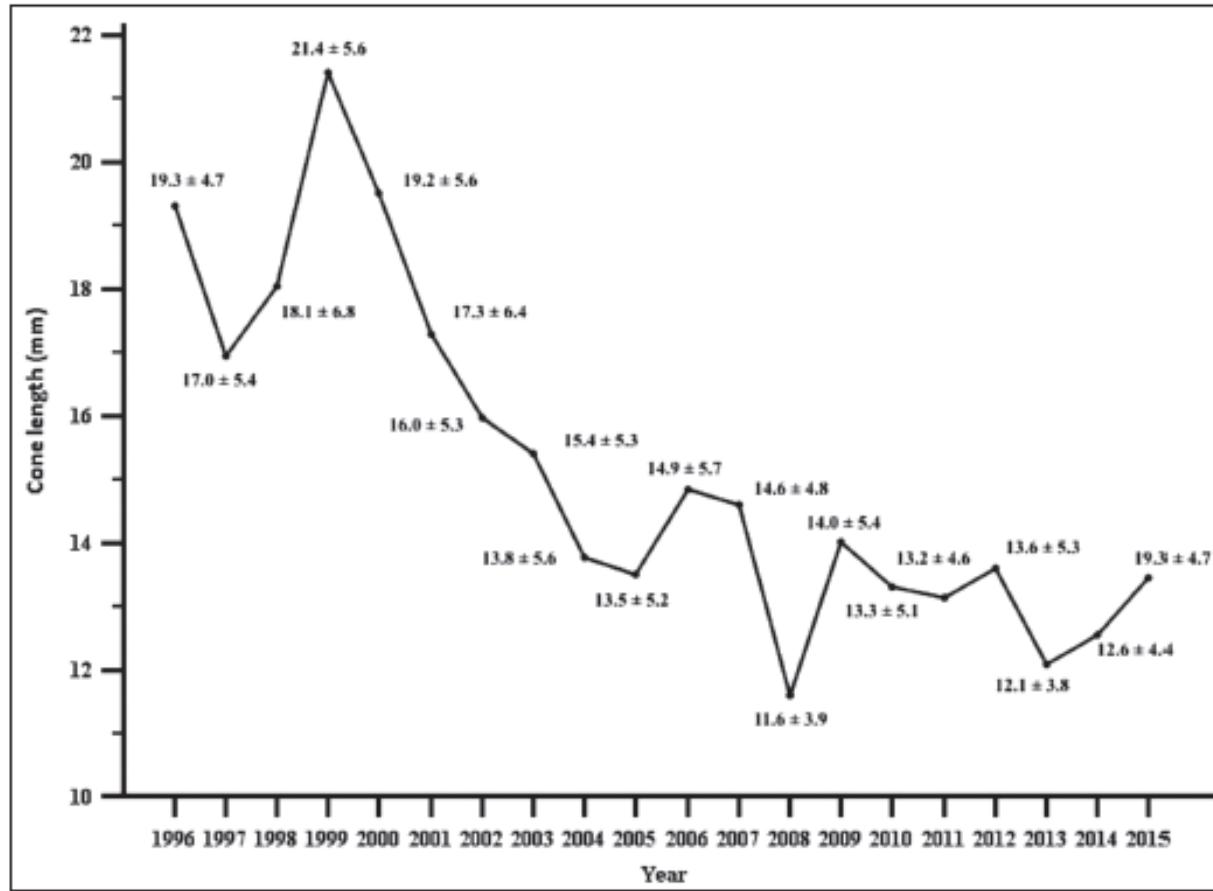


Figure 1. Length of cone excisions (expressed as mean \pm SD) in the entire study cohort ($n = 1270$) considering the year of the procedure.

Progressiva riduzione dell'impatto clinico dei trattamenti escisionali negli anni - maggiore attenzione degli operatori, riduzione delle dimensioni dei campioni

What is the value of pre-surgical variables in addition to cone dimensions in predicting cone margin status?

Luca Giannella, Jacopo Di Giuseppe, Sonia Prandi, Giovanni Delli Carpini, Dimitrios Tsiroglou, Andrea Ciavattini



Accepted Article

Objective: Previous studies have shown associations between independent pre-conization variables (e.g. smoking, age, cytological grade, menopause) and positive or negative cone margins. However, it is not clear if these pre-surgical variables add predictive value to cone dimensions in the prediction of cone margin status. This study aimed to compare different models predicting positive ecto- or endocervical margins to assess whether pre-conization variables provide significant added value compared with cone dimensions alone.

Study design: One hundred and sixty-one consecutive women with high-grade cervical intraepithelial neoplasia on cone specimens were analysed retrospectively. The sample was divided into women with positive ecto- or endocervical cone margins and women with negative ecto- or endocervical cone margins. Pre-conization clinical features, cone volume and cone length were included among the study variables. Multivariate stepwise regression analysis was used to create different models predicting incomplete cervical excision. The added value of pre-conization predictors was measured with receiver operating characteristic (ROC) curve comparisons.

Results: Multivariate analysis showed that a positive ectocervical margin was significantly associated with low-grade cervical cytology [odds ratio (OR)=0.25, 95% confidence interval (CI) 0.09–0.70] and **cone length (OR=0.69, 95% CI 0.58–0.82, criterion <9 mm)**. The area under the curve (AUC) of the combined model for prediction of a positive ectocervical margin was 0.78 (95% CI 0.70– 0.84, $p<0.001$). A positive endocervical margin was associated with **cone length (OR=0.78, 95% CI 0.65–0.93, criterion <9 mm)** and age (OR=1.07, 95% CI 1.02–1.11, criterion ≥ 45 years). The AUC of the combined model for prediction of positive endocervical margin was 0.75 (95% CI 0.66–0.82, $p<0.001$). Comparison of ROC curves showed that the addition of pre-conization variables to cone length did not yield significant predictive results for either ecto- or endocervical cone margins ($p=0.228$ and 0.349, respectively).

Conclusions: The addition of pre-conization clinical variables to cone dimensions did not improve the prediction of cone margin status significantly in the study cohort. **Among cone dimensions, cone length was the best predictor of cone margin status.**

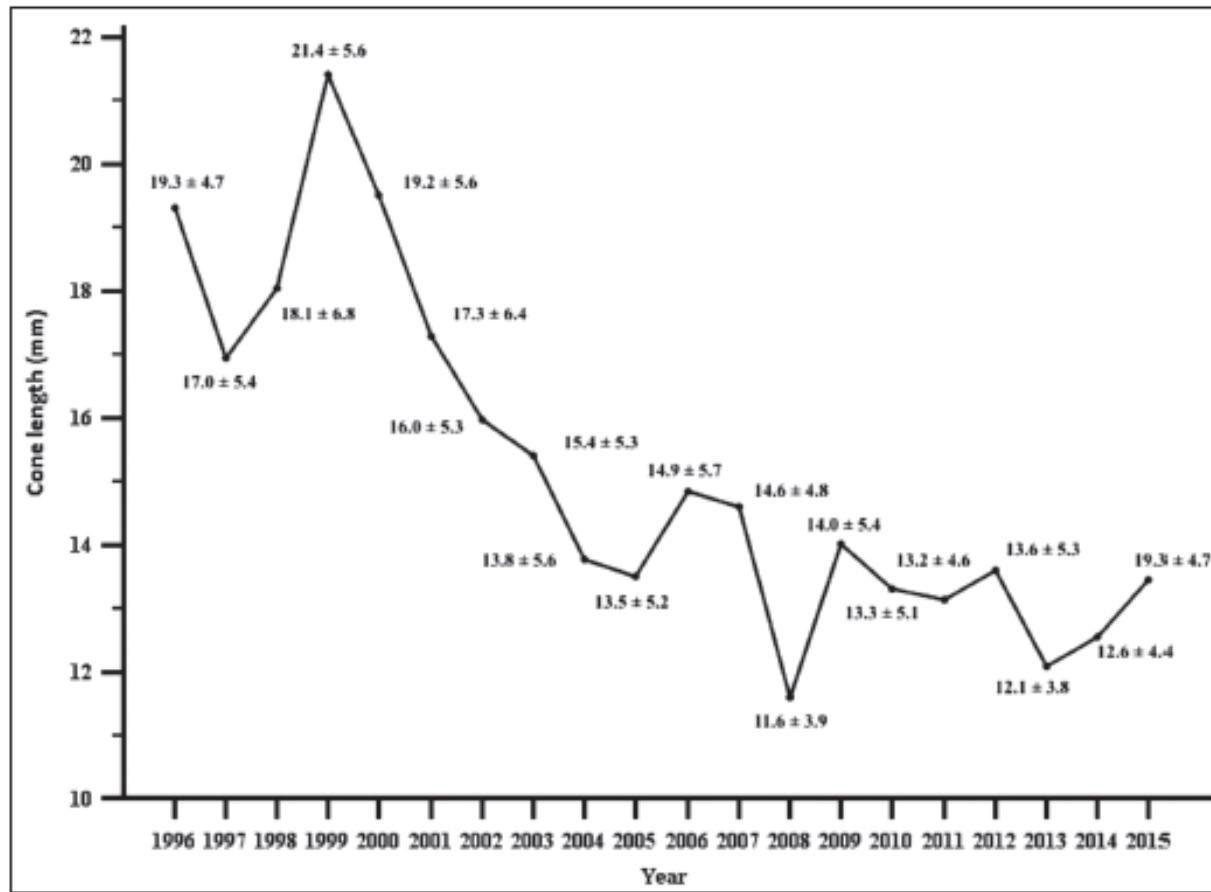


Figure 1. Length of cone excisions (expressed as mean \pm SD) in the entire study cohort ($n = 1270$) considering the year of the procedure.

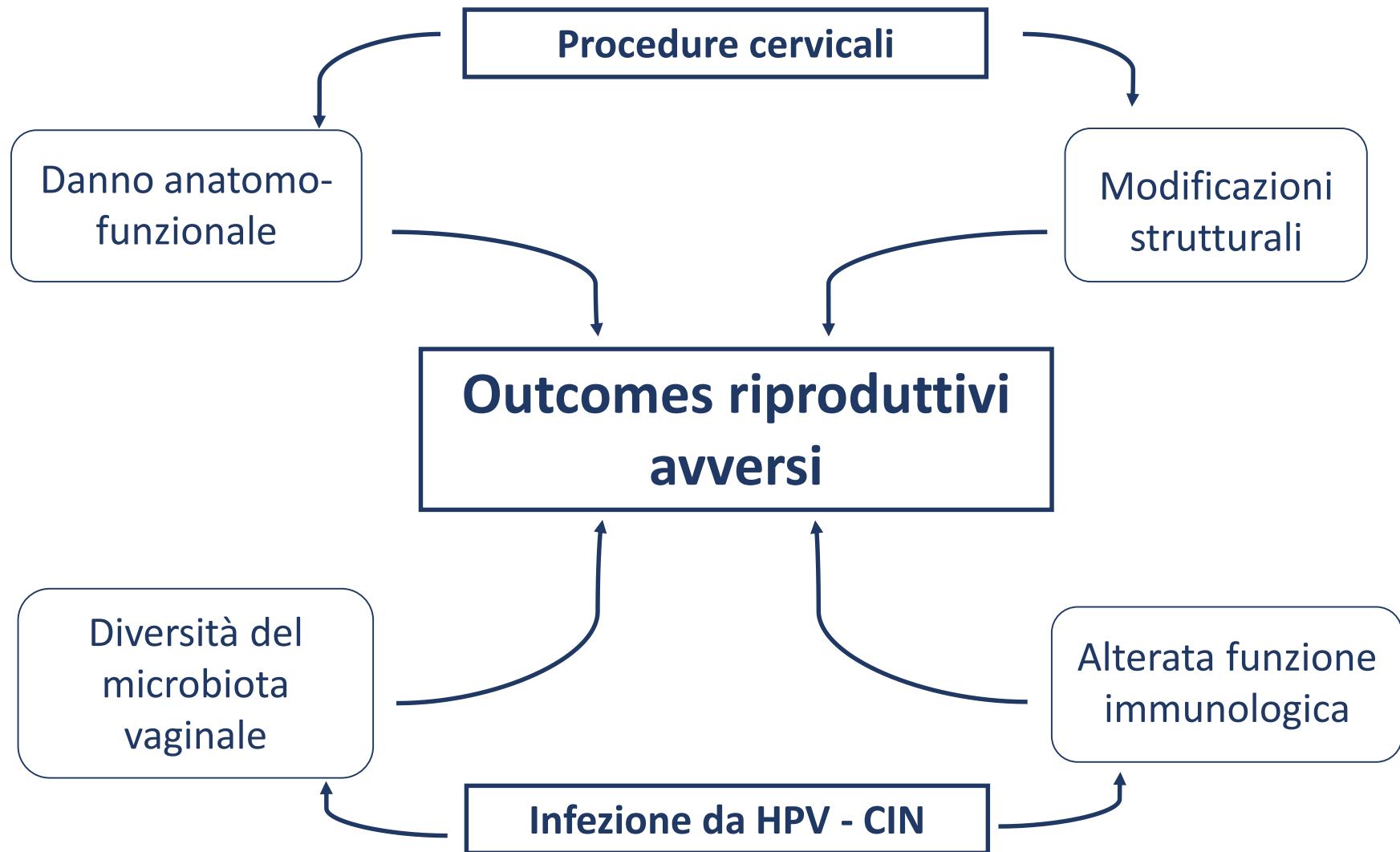
Progressiva riduzione dell'impatto clinico dei trattamenti escisionali negli anni - maggiore attenzione degli operatori, riduzione delle dimensioni dei campioni

..... ma quanti parti pretermine sono dovuti esclusivamente ad una pregressa escissione cervicale?

Take home messages

- Il trattamento escisionale cervicale può associarsi ad **outcomes ostetrici sfavorevoli**, sia materni che fetal
 - i dati sono maggiormente suggestivi verso il rischio di parto pretermine, tuttavia la qualità delle evidenze è bassa
- Il **danno anatomo funzionale** cervicale è il principale responsabile dell'aumento del rischio di parto pretermine ed esso è direttamente correlato alla **profondità** del cono escluso
- Fondamentale sensibilizzare gli operatori nel **ridurre le dimensioni** del **cono da escludere**, in particolare nelle pazienti con desiderio di fertilità, al fine di contenere/minimizzare il rischio di **outcome ostetrici avversi** – 10 mm
- Opportunità di un **counselling specifico** sulle **implicazioni riproduttive** dei **trattamenti**, da effettuarsi in fase pre trattamento, nella popolazione desiderosa di prole

Fattori determinanti



Microbiota vaginale

Il **microbiota vaginale** gioca un ruolo fondamentale nella prevenzione della vaginosi batterica, delle MST, delle infezioni urinarie e dell'HIV



Il **microbiota vaginale** presente nella vaginosi batterica è associato ad un aumentato rischio di **minaccia di parto pretermine ma non di un vero parto pretermine**

... 83% delle donne con disbiosi vaginale alla 16° settimana di gestazione partorirà oltre la 34° settimana

Dunlop AL, Mulle JG, Ferranti EP, Edwards S, Dunn AB, Corwin EJ. Maternal Microbiome and Pregnancy Outcomes That Impact Infant Health: A Review. *Adv Neonatal Care*. 2015 Dec;15(6):377-85

Peelen, M. J., Luef, B. M., Lamont, R. F., de Milliano, I., Jensen, J. S., Limpens, J. et al (2019). *The influence of the vaginal microbiota on preterm birth: A systematic review and recommendations for a minimum dataset for future research*. *Placenta* 2019.



Check for updates

RESEARCH ARTICLE

HPV infection and pre-term birth: a data-linkage study using Scottish Health Data [version 1; peer review: 3 approved]

Marian C. Aldhous¹, Ramya Bhatia², Roz Pollock³, Dionysis Vragkos³,
Kate Cuschieri⁴, Heather A. Cubie², Jane E. Norman ¹, Sarah J. Stock ⁵

Conclusions: HPV-associated high-grade cervical disease was associated with preterm birth, but there were no associations with HR HPV-infection or low-grade cervical disease. Thus HPV-infection alone (in the absence of cervical disease) does not appear to be an independent risk factor for preterm birth. For women who have undergone treatment for CIN and become pregnant, these results demonstrate the need to monitor for signs of preterm birth.

Microbiota vaginale

Inoltre l'infezione da **HPV** e le **lesioni displastiche** cervicali ad essa correlate sono un fattore di rischio indipendente.

...cervical infection of **high risk HPV** detected using HPV DNA testing was associated with the findings of **thrombosis and villitis in placental examinations** and was strongly associated with **preterm birth** ...

Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PP, Arbyn M, Bennett P, Paraskevaidis E. *Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease*. Cochrane Database Syst Rev. 2017 Nov 2;11:CD012847. doi: 10.1002/14651858.CD012847.

Zuo Z, Goel S, Carter JE. *Association of cervical cytology and HPV DNA status during pregnancy with placental abnormalities and preterm birth*. Am J Clin Pathol. 2011 Aug;136(2):260-5